

Citation for published version:

Combe, B, Behrens, F, McHugh, N, Brock, F, Kerkmann, U, Kola, B & Gallo, G 2016, 'Comparison of etanercept monotherapy and combination therapy with methotrexate in psoriatic arthritis: results from 2 clinical trials', *The Journal of Rheumatology*, vol. 43, no. 6, pp. 1063-1067. <https://doi.org/10.3899/jrheum.151290>

DOI:

[10.3899/jrheum.151290](https://doi.org/10.3899/jrheum.151290)

Publication date:

2016

Document Version

Peer reviewed version

[Link to publication](#)

This is a pre-copy-editing, author-produced PDF of an article accepted for publication in *The Journal of Rheumatology* following peer review. The definitive publisher-authenticated version Combe, B, Behrens, F, McHugh, N, Brock, F, Kerkmann, U, Kola, B & Gallo, G 2016, 'Comparison of Etanercept Monotherapy and Combination Therapy with Methotrexate in Psoriatic Arthritis: Results from 2 Clinical Trials' *The Journal of Rheumatology*, is available online at: <http://dx.doi.org/10.3899/jrheum.151290>

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Title

Comparison of Etanercept Monotherapy and Combination Therapy With Methotrexate in Psoriatic Arthritis: Results From Two Clinical Trials

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This study was sponsored by Pfizer.

Conflicts of interest

Dr. Combe has received honoraria from Abbvie, BMS, Janssen, Lilly, MSD, Pfizer, Roche-Chugai, and UCB, and research grants from Pfizer, Roche-Chugai, and UCB. Dr. Behrens has received honoraria from Abbvie, Biotest, Celgene, Chugai, Janssen, Lilly, MSD, Pfizer, and UCB, and research grants from Chugai, Pfizer, and Roche. Dr. McHugh has received honoraria from Abbvie, Pfizer, Novartis, and Celgene, and research grants from Abbvie, Pfizer, and Celgene. Ms. Brock is an employee of Quanticate, contracted and paid by Pfizer to provide

statistical input to the study and manuscript. Dr. Kerkmann was a former employee of Pfizer.

Drs. Kola and Gallo are employees of Pfizer.

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Short title: Etanercept mono- vs combination therapy in PsA

ABSTRACT

Objective. To evaluate clinical/functional outcomes associated with etanercept monotherapy vs combination therapy in psoriatic arthritis (PsA).

Methods. Data from PsA patients who received etanercept alone (n = 322) or combined with methotrexate (n = 152) for 24 weeks in 2 placebo-controlled clinical trials were summarized across studies.

Results. Similar proportions of patients in monotherapy- and combination-therapy groups achieved PsARC (80% and 83%) and ACR20 (70%, both); numerically higher proportions receiving monotherapy achieved ACR50 (55% vs 48%) and ACR70 (35% vs 27%). Little between-group difference was observed in DAS28-CRP, PASI, and HAQ-DI improvement.

Conclusions. Etanercept with and without methotrexate provided similar benefits in active PsA.

Key Indexing Terms: psoriatic arthritis, biologic, DMARD, etanercept, methotrexate

INTRODUCTION

In patients with chronic inflammatory diseases, anti-tumor necrosis factor (TNF) agents are often administered in combination with the synthetic disease-modifying antirheumatic drug (DMARD) methotrexate to enhance clinical outcomes, reduce the risk of immunogenicity, and improve drug survival (1). In rheumatoid arthritis, evidence from comparative controlled trials of anti-TNF agents and current treatment guidelines strongly support use of such combination therapy, as it was proven more effective than anti-TNF monotherapy (2-6). Randomized controlled trials in psoriatic arthritis (PsA) have evaluated the efficacy and safety of etanercept, adalimumab, and infliximab as monotherapy and as add-on therapy to ongoing methotrexate treatment (7-13). However, to date, no study has directly compared outcomes in patients receiving anti-TNF monotherapy or anti-TNF–methotrexate combination therapy. Current treatment guidelines do not include recommendations on the appropriate use of biologics as monotherapy or combined with methotrexate (14-16).

Etanercept has been studied in 2 main placebo-controlled trials in PsA (7,9). In a 12-week, single-center trial (9), patients with active disease despite stable doses of methotrexate were permitted to remain on the nonbiologic DMARD and were randomized to etanercept 25 mg twice weekly (BIW) subcutaneously or placebo. At week 12, 87% and 23% of patients in the etanercept and placebo groups, respectively, met the PsA response criteria (PsARC). In a larger multicenter study (7), in which background methotrexate was also allowed but not mandatory, at 12 and 24 weeks, PsARC response was achieved by 72% and 70% of patients receiving etanercept 25 mg BIW compared with 31% and 23% of those receiving placebo, respectively. In the Psoriasis Randomized Etanercept Study in Subjects with Psoriatic Arthritis (PRESTA), patients were randomized to receive etanercept 50 mg BIW or 50 mg once weekly (QW) subcutaneously for 12 weeks (8); patients continued treatment with etanercept 50 mg QW open label for 12 additional weeks, with the option of remaining on stable doses of methotrexate through both study phases. In PRESTA, similar proportions of patients in the BIW and

QW groups achieved PsARC response (i.e., 77% vs 76%, and 82% and 80%, respectively) at weeks 12 and 24.

As the design and patient populations of the latter 2, 24-week clinical trials were relatively similar, post hoc analyses were conducted using pooled data from the trials to evaluate potential differences in clinical and functional outcomes in patients with PsA who received etanercept with and without methotrexate (7,8).

METHODS

Study design and patients

Adult patients (aged ≥ 18 years) with active PsA who participated in the selected studies were divided into 2 groups: patients who received etanercept 25 mg BIW (7) or 50 mg QW (8) without concomitant methotrexate were included in the monotherapy group, and patients who received etanercept 25 mg BIW (7) or 50 mg QW (8) with concomitant methotrexate were included in the combination therapy group. (The etanercept 50-mg BIW group in the PRESTA study (8) was excluded from these analyses.) In the combination therapy group, methotrexate could have been continued at stable dosages of ≤ 25 mg/week (4) or ≤ 20 mg/week (8). Patients in this group were required to have received etanercept plus methotrexate on at least 1 occasion, but their therapy was not restricted exclusively to this combination for the 24-week study period.

Assessments

Clinical efficacy was measured by comparing the proportions of patients who achieved PsARC, American College of Rheumatology (ACR) improvements of 20% (ACR20), 50% (ACR50), and 70% (ACR70) and Psoriasis Area Severity Index (PASI) improvement of 75% (PASI75) in the etanercept monotherapy and combination therapy groups across both studies after 24 weeks of treatment.

Assessments of clinical efficacy in joints and skin also included improvement from baseline to week 24

in Disease Activity Score in 28 joints (DAS28)–C-reactive protein (CRP) and PASI. Physical function was measured using the Health Assessment Questionnaire Disability Index (HAQ-DI).

Statistical analysis

Demographic and disease activity characteristics of patients in the monotherapy and combination therapy groups (intent-to-treat [ITT] populations) across both studies at baseline are summarized using descriptive statistics, as are data for categorical and continuous efficacy/functional variables.

Percentage response at 24 weeks to PsARC, ACR20, 50, 70, and PASI75 were calculated for each treatment arm. Mean response at 24 weeks and the 24-week change from baseline were calculated for DAS28-CRP, PASI, and HAQ-DI for each treatment arm. As the treatment comparison was not part of the randomized design of the original studies, no formal hypothesis testing was applied; 95% confidence intervals (CIs) were calculated to assist with interpretation of the estimated values.

RESULTS

Patients

A total of 322 ITT patients were included in the etanercept monotherapy group and 152 ITT patients in the combination therapy group. In the monotherapy group, 56 patients received etanercept 25 mg BIW (7) and 266 patients received etanercept 50 mg QW (8); in the combination therapy group, 45 patients received the bi-weekly dosage (7) and 107 patients, the QW dosage (8). The mean weekly methotrexate dosage was 13.8 (SD, 4.9) mg in the combination therapy group.

Baseline demographic and disease characteristics were similar across groups (**Table 1**). Duration of PsA and psoriasis in patients receiving etanercept with and without methotrexate was 8.2 and 9.0 years, and 18.4 and 17.5 years, respectively.

Clinical/functional outcomes

Clinical efficacy in joints was similar for the monotherapy and combination therapy regimens over 24 weeks based on most outcomes measured. PsARC was achieved by 80.3% (95% CI, 75.8, 84.8) and 82.6% (76.5, 88.8) of patients in the monotherapy and combination therapy groups, respectively, and an ACR20 response in approximately 70% (70.5% [65.2, 75.8]; 69.9% [62.4, 77.5]) in both groups (**Figure 1**). Numerically higher proportions of patients in the monotherapy group achieved ACR50 (54.9% [49.1, 60.6] vs 48.3% [40.1, 56.4]) and ACR70 (34.7% [29.2, 40.2] vs 26.6% [19.3, 33.8]) responses. Similar mean improvements in DAS28 (-1.85 [-2.03 , -1.68] and -1.84 [-2.04 , -1.64]) were also observed in these groups from baseline to week 24 (**Figure 2A**).

Clinical responses in skin were also comparable. A PASI75 response was achieved by 59.7% (54.0, 65.5) and 58.6% (50.1, 67.1) of patients receiving monotherapy and combination therapy, respectively (**Figure 1**). Mean improvements in PASI (-13.60 [-14.73 , -12.47] and -12.18 [-13.84 , -10.53]) were similar between groups from baseline to week 24 (**Figure 2B**). In addition, minimal difference in improvement in HAQ-DI (-0.51 [-0.58 , -0.45] and -0.59 [-0.69 , -0.50]) was observed between the groups from baseline to week 24 (**Figure 2C**).

DISCUSSION

In these analyses, patients with active PsA who had been treated with etanercept with or without methotrexate achieved similar improvements in clinical and functional outcomes after 24 weeks of treatment. Methotrexate co-administration had minimal impact on the efficacy of etanercept in terms of the joints, skin, or physical function in PsA. Our findings are not in agreement with evidence from controlled trials and management guidelines in rheumatoid arthritis that support use of biologic therapy in combination with methotrexate rather than biologic monotherapy due to superior efficacy (2-6), but they are consistent with results of systematic reviews of randomized trials in PsA (17), registries

(18,19), and observational studies (20), which reported similar responses to anti-TNF agents administered alone and with methotrexate in patients with PsA in a real-world setting.

In systematic reviews, anti-TNF agents combined with methotrexate in PsA were not found to provide greater improvement in clinical symptoms than anti-TNF monotherapy, but combination therapy appeared to play a role in prolonging anti-TNF therapy continuation and decreasing side effects (17,21). Patients treated with anti-TNF agents and concomitant methotrexate in the Southern Swedish Arthritis Treatment Group registry had significantly better drug survival, primarily because of fewer dropouts owing to adverse events, than those treated with anti-TNF monotherapy (18). In the British Society for Rheumatology Biologics Register and the Norwegian longitudinal observational study on DMARDs, concomitant methotrexate was not associated with an advantage over anti-TNF monotherapy in terms of efficacy. However, drug survival was superior in infliximab-treated and adalimumab-treated patients who received methotrexate but not in etanercept-treated patients (19,20), suggesting that outcomes may be dependent on the individual biologic assessed. Similarly, in the observational PROVE study, drug survival over 5 years in etanercept-treated patients with PsA was not significantly affected by use of methotrexate (22). Drug survival may be influenced by multiple factors, including patient adherence, treatment efficacy, safety and tolerability, and the development of anti-drug antibodies. Anti-drug antibodies against the anti-TNF monoclonal antibodies infliximab and adalimumab have been shown to substantially reduce response rates, an effect that is diminished by concomitant methotrexate; in contrast, antibodies against the fusion receptor protein etanercept are rarely detected (23). Although immunogenicity was not analyzed in the aforementioned studies, this factor may explain, at least in part, the different drug survival profiles associated with these agents.

Among the strengths of these analyses are the large number of patients included and the use of randomized controlled studies. However, these studies were not designed or sized to address differences in clinical outcomes between anti-TNF agents used as monotherapy or in combination with methotrexate, which is a limitation of the analyses. Patients were not randomized to receive anti-TNF

monotherapy or combination therapy, introducing potential bias. In addition, the study duration of 24 weeks was not sufficient to identify long-term treatment effects.

In conclusion, methotrexate administered in combination with the anti-TNF agent etanercept in patients with PsA may not provide significantly greater improvement in arthritis or psoriasis symptoms than etanercept monotherapy. This finding may be particularly important in patients with intolerance or contraindications to methotrexate treatment. Further research is warranted to better understand the potential advantages and disadvantages of methotrexate use with anti-TNF therapy for PsA.

ACKNOWLEDGMENTS

Editorial/medical writing support was provided by Kim Brown, PhD, and Donna McGuire of Engage Scientific Solutions and was funded by Pfizer.

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Figure Legends

Figure 1. Proportions of patients (95% CI) achieving clinical responses (joint and skin) at week 24.

Figure 2. Mean changes (95% CI) from baseline to week 24. A. DAS28. B. PASI. C. HAQ-DI.